ORIGINAL ARTICLE

High Levels of Dopamine D_2 Receptors in Unaffected Members of Alcoholic Families

Possible Protective Factors

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Context: Predisposition to alcoholism is likely an interaction between genetic and environmental factors that confer vulnerability and protection. Alcoholic subjects have low levels of dopamine D_2 receptors in striatum, and increasing D_2 receptor levels in laboratory animals reduces alcohol consumption.

Objectives: To test whether high levels of D_2 receptors may be protective against alcoholism and whether this is mediated by their modulation of activity in orbitofrontal cortex and cingulate gyrus (regions involved in salience attribution, emotional reactivity, and inhibitory control).

Design: Research (nonalcoholic subjects with a family history of alcoholism) and comparison (nonalcoholic subjects with a negative family history) sample.

Setting: Outpatient setting.

Participants: Fifteen nonalcoholic subjects who had an alcoholic father and at least 2 other first- or second-degree relatives who were alcoholics (family-positive group) and 16 nonalcoholic controls with no family history of alcoholism (family-negative group).

Main Outcome Measures: Results of positron emission tomography with raclopride C 11 to assess D_2 receptors and with fludeoxyglucose F 18 to assess brain glucose metabolism (marker of brain function). Personality measures were obtained with the Multidimensional Personality Questionnaire.

Results: Availability of D_2 receptors was significantly higher in caudate and ventral striatum in family-positive than family-negative subjects. In family-positive but not family-negative subjects, striatal D_2 receptors were associated with metabolism in anterior cingulate (Brodmann area 24/25) and orbitofrontal (Brodmann area 11) and prefrontal (Brodmann area 9/10) cortices, and with personality scores of positive emotionality.

Conclusions: The higher-than-normal D_2 receptor availability in nonalcoholic members of alcoholic families supports the hypothesis that high levels of D_2 receptors may protect against alcoholism. The significant associations between D_2 receptors and metabolism in frontal regions involved with emotional reactivity and executive control suggest that high levels of D_2 receptors could protect against alcoholism by regulating circuits involved in inhibiting behavioral responses and in controlling emotions.

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GENETIC FACTORS HAVE A powerful influence on alcoholism, accounting for approximately 50% to 60% of the population variance.[1] Genetic associations are both direct (ie, via genes that regulate alcohol's metabolism and its reinforcing or aversive effects)[2,3] and indirect (ie, via genes that affect personality characteristics and externalizing disorders).[4] However, it is also evident that environmental factors as well as gene-environment interactions play a crucial role in vulnerability and in protection against alcoholism.[5,6]

Several neurotransmitters appear to mediate alcohol's reinforcing and addictive effects (ie, γ-aminobutyric acid [GABA], dopamine [DA], opioids, serotonin, and *N*-methyl-D-aspartate).[7] Of these, DA is believed to play an important role in alcohol's reinforcing effects.[8,9] The DA D_2 receptor is one of the DA receptor subtypes involved in transmitting these reinforcing signals.[10,11] This fact has been documented in a variety of ways; for example, D_2 receptor antagonist drugs decrease reinforcing responses to alcohol in rodents[12] and in humans.[13] Also, studies have shown differences in D_2 receptor levels be-

tween rat strains that differ in their preferences for alcohol,[10,14] and D_2 receptor knockout mice exhibit reduced reinforcing responses to alcohol.[15] In humans, imaging studies have shown that differences in D_2 receptor availability in nonalcoholic subjects are associated with differences in sensitivity to the intoxicating effects of alcohol.[16] Levels of D_2 receptor may also be involved with alcohol addiction, as evidenced by imaging and postmortem studies showing reductions in D_2 receptor levels in the striatum from the brains of alcoholic subjects.[17-20] Because low D_2 receptor availability in striatum has also been documented in other drug addictions when compared with non–drug-abusing control subjects, it has been postulated that this reduction may render an individual more vulnerable to substance abuse.[21] However, an alternative explanation could be that the higher levels of D_2 receptor in striatum observed in non–drug-abusing controls could reflect a protective effect against substance abuse in these subjects. This hypothesis is supported by imaging studies showing that controls with high D_2 receptor availability in striatum report aversive responses to stimulant drugs.[22,23] Also, preclinical studies show that overexpression of D_2 receptor in nucleus accumbens markedly reduces alcohol intake,[24,25] even in selectively bred alcohol-preferring P rats.[25]

Herein we test the hypothesis that high D_2 receptor availability may be protective against alcohol abuse. We reasoned that the population of individuals who, despite a dense positive family history of alcoholism (biological father and at least 2 other first- or second-degree relatives), are not alcoholic may be enriched with protective factors, including high D_2 receptor availability. Therefore, we selected subjects who met these criteria for our study. Of course, this reasoning also suggests that the population of individuals with a positive family history and who are alcoholic themselves may lack protective factors, but we did not select this group as a comparison because long-term alcohol use can alter striatal D_2 receptor expression,[26] which would interfere with the identification of variables that protect against alcoholism.

Positron emission tomographic (PET) imaging with carbon 11 (^{11}C)–labeled raclopride was used to measure D_2 receptor availability.[27] In addition, we used fludeoxyglucose F 18 (FDG) to measure regional brain glucose metabolism (marker of brain function),[28] since we also hypothesized that protection is mediated by D_2 receptor modulation of the activity in the orbitofrontal cortex (OFC) and anterior cingulate gyrus (CG), which are brain regions involved with salience attribution and inhibitory control.[29] Indeed, in addicted subjects, lower-than-average D_2 receptor availability is associated with lower-than-average metabolism in OFC and CG (reviewed by Volkow et al[30]), and in alcoholic subjects, low metabolism in these regions persists after protracted detoxification and may underlie vulnerability to relapse.[31] We also used the Multidimensional Personality Questionnaire[32] to investigate whether a D_2 receptor protective effect is associated with personality characteristics that decrease the likelihood of alcohol abuse (positive emotionality).

METHODS

SUBJECTS

Family-positive (FP) subjects were 15 individuals (1 woman and 14 men; mean±SD age, 24±3 years) who had an alcoholic biological father (according to *DSM- IV*) with an early-onset history of alcoholism (before 25 years of age) and at least 2 other first- or second-degree relatives who were or had been alcoholics. Subjects were excluded if they had a previous or current history of abuse of or dependence on alcohol and/or other drugs of abuse (except nicotine), or any other *DSM-IV* Axis I diagnosis of mental illness and/or neurologic illnesses in themselves or in a first-degree relative (except for a family history of alcoholism), or if they had medical illnesses and/or were taking any prescribed medications. Nondrinkers (consuming alcohol less than once every year) were also excluded because we wanted to exclude subjects who may have not become alcoholics because they had minimal or no exposure to alcohol. Family-negative (FN) subjects were 16 controls (2 women and 14 men, aged 26±4 years). Subjects were excluded if they had a family history of alcoholism or drug abuse in first- and/or second-degree relatives. Otherwise, criteria were as for FP subjects.

As part of the evaluation procedure, subjects underwent physical, psychiatric, and neurologic examinations. A standardized interview was used to ensure that subjects fulfilled the inclusion and exclusion criteria. Routine laboratory tests were performed, as was a random urine test to exclude the use of psychoactive drugs. Subjects were instructed to discontinue any over-the-counter medication 2 weeks before the PET scan and to refrain from drinking alcohol the week before the PET scan. Cigarettes, food, and beverages (except for water) were discontinued at least 4 hours before the study. This study was approved by the institutional review board at Brookhaven National Laboratory. After the procedure was explained, written informed consent was obtained from each subject.

PERSONALITY MEASURES

Participants completed the Multidimensional Personality Questionnaire.[32] The personality measures were scored for the 3 superfactors of positive emotionality (or extraversion), negative emotionality (neuroticism), and constraint. Positive emotionality is a combination of scores for the scales of well-being, social potency, achievement (including motivation), and social closeness. Negative emotionality is a combination of scores for the scales of stress reaction, alienation, and aggression. The constraint factor is a combination of scores for the scales of self-control, harm avoidance, and traditionalism.

PET STUDIES

The PET studies were carried out with an HR+ tomograph (resolution, 4.5×4.5×4.5-mm full-width at half-maximum, 63 sections; Siemens Medical Solutions, Knoxville, Tenn) in 3-dimensional dynamic acquisition mode. Subjects underwent scanning with [^{11}C]raclopride and with FDG. Methods for positioning of subjects, catheterizations, transmission scans, and blood sampling and analysis have been published for [^{11}C]raclopride [27] and for FDG.[33] Briefly, for [^{11}C]raclopride, emission scans were started immediately after injection of 4 to 8 mCi (148-296 MBq) (specific activity was 0.5-1.5 Ci/μmol [1.85-5.55×10^{10} Bq/μmol] at the end of bombardment), and a total of 20 emission images were obtained from the time of injection up to 54 minutes. Arterial sampling was used to measure total carbon 11 and unchanged radiotracer in plasma. For FDG, a 20-minute emission scan was started 35 minutes after injec-

tion of 4 to 6 mCi (148-222 MBq) of FDG, and arterialized blood was used to measure FDG in plasma. Metabolic rates were computed by means of an extension of Sokoloff's model.[34] The emission data for all of the scans were corrected for attenuation and reconstructed with filtered back projection.

IMAGE ANALYSIS AND STATISTICS

For region identification for the [^{11}C]raclopride images, the time frames from dynamic images taken from 10 to 54 minutes were summed, and the summed image was resectioned along the intercommissural plane (anterior commissure–posterior commissure line). Planes were added in groups of 2 to obtain 12 planes encompassing the caudate, putamen, ventral striatum, and cerebellum for region-of-interest (ROI) placement. The caudate, putamen, ventral striatum, and cerebellum were measured on 4, 3, 1, and 2 planes, respectively, and right and left regions were averaged. These regions were then projected to the dynamic scans to obtain concentrations of carbon 11 vs time. These time-activity curves for tissue concentration were used to calculate distribution volume ratios in caudate, putamen, and ventral striatum by means of a graphical analysis technique for reversible systems.[35] The distribution volume ratio, which is the ratio of the distribution volume (DV) in striatum to that in cerebellum and which corresponds to $f2 \times B_{max}/K_d + 1$ (where f2 indicates free fraction in the first tissue compartment; B_{max}, receptor concentration; and K_d, affinity), was used as an estimate of D_2 receptor availability.[36] Differences in D_2 receptor between FP and FN subjects were tested with unpaired *t* tests.

The metabolic images were analyzed by statistical parametric mapping (SPM).[37] For this purpose, the images were spatially normalized by means of the template provided in the SPM 99 package (Statistical Parametric Mapping, Cambridge, England), then normalized to the mean metabolic activity for the whole brain (mean of all voxels within the brain) and subsequently smoothed with a 16-mm isotropic gaussian kernel. Independent (unpaired) *t* tests were used to compare the images between FP and FN subjects. We hypothesized, on the basis of our previous findings,[38] that FP subjects would have decreases in baseline cerebellar and hippocampal metabolism. In addition, we obtained ROIs from the metabolic images by means of an automated ROI extraction method that is based on the standard brain template of the Talairach atlas.[39] First, to eliminate variations across individuals' brains, the FDG images were mapped into the Montreal Neurological Institute standard brain space by means of the spatial normalization package provided in SPM. To perform the ROI calculations, we produced a map that covered all of the corresponding voxels for a given region (following the coordinates in the Talairach Daemon software[40-42]) into the normalized FDG PET image.[43] This automated ROI method was validated by comparing the metabolic measures obtained with the manually drawn ROIs (Y_i) and those obtained with the automated ROI (X_i) from FDG images of 35 subjects.[44] The correlations between the 2 methods were very high and ranged between $r=0.86$ and $r=0.99$. The difference between mean (Y_i) and mean (X_i) did not differ significantly from 0.

To assess the correlations between D_2 receptor and regional metabolism, we determined Pearson *r* values between D_2 receptor availability (B_{max}/K_d) in caudate, putamen, and ventral striatum and the metabolic measures (for each voxel by SPM). The statistically significant *r* values were overlaid on a magnetic resonance imaging structural image. The findings from SPM were corroborated by measuring the correlations between D_2 receptor and the metabolic values obtained with independently drawn ROIs.

To assess the correlations between personality measures and striatal D_2 receptors, we determined Pearson *r* values between the 3 factor scores (positive emotionality, negative emotionality, and constraint) and D_2 receptor availability in caudate, putamen, and ventral striatum. To assess the correlations between personality measures and regional metabolism, we determined Pearson *r* values between the 3 factor scores and the metabolic measures (for each voxel by SPM). The statistically significant *r* values were overlaid on a magnetic resonance imaging structural image. The significant correlations were then corroborated by means of the independently drawn ROI.

In consideration of the "multiple comparison problem," we set the level of significance for a priori hypotheses to $P<.05$: (1) increases in FP subjects in D_2 receptor availability in striatum; (2) correlations between D_2 receptor availability and metabolism in OFC, CG, and prefrontal cortex; (3) correlations between D_2 receptor availability and personality measures of positive emotionality; and (4) decreases in FP subjects in baseline cerebellar and hippocampal metabolism. For the exploratory analyses, significance was set to $P<.005$ (corrected for multiple comparisons; clusters ≥100 voxels) and corroborated with independently drawn ROI.

Table 1. Subject Demographics

	FP (n = 15)	FN (n = 16)
Age, mean ± SD, y	24 ± 3	26 ± 4
Sex, No. F/M	1/14	2/14
Education, mean ± SD, y	14 ± 2	13 ± 2
Socioeconomic status, mean ± SD*	43 ± 9	37 ± 12
Ethnicity, No.		
African American	8	8
White	2	3
Hispanic	5	4
Asian	0	1
Smoking histories, No. of subjects	4	3
Current smoking, No. of subjects	3	2
IQ verbal, mean ± SD†	104 ± 15	100 ± 14
Depression score, mean ± SD‡	7.1 ± 5	7.5 ± 7

Abbreviations: FN, family negative; FP, family positive.
*Measured by the Hollingshead Two Factor Index of Social Position.[45]
†Estimated by the Wide Range Achievement Test reading scaled score.
‡Self-reported depression as measured by the Beck Depression Inventory II.[46]

RESULTS

DEMOGRAPHICS AND PERSONALITY MEASURES

There were no differences in age, sex, education, socioeconomic status, ethnicity, smoking histories, verbal IQ, or scores on the Beck Depression Inventory between the 2 groups of subjects (**Table 1**). The comparison of the personality measures, which were completed by 13 FP and 11 FN subjects, showed significant differences between the groups. The scores for positive emotionality were lower in FP than in FN subjects (46.8±10 vs 56.3±8; $P=.02$) and, within this factor, showed lower scores on the well-being (6.9±3 vs 9.7±1; $P=.007$) and the achievement (12.4±4 vs 16.4±2; $P=.006$) scales. The scores on the constraint factor did not differ between FP and FN subjects (44.0±14 vs 52.8±9; $P=.10$) but showed a trend toward lower scores on the self-control scale in FP subjects (13.4±5 vs 17.7±5; $P=.06$). Scores on negative emotionality did not differ between groups.

Table 2. Estimates of K_1 and B_{max}/K_d Measures for D_2 Receptors in FP and FN Subjects

	Mean ± SD			
	Cerebellum	Caudate	Putamen	Ventral Striatum
K_1				
FP	0.33 ± 0.08	0.44 ± 0.08	0.48 ± 0.09	0.44 ± 0.08
FN	0.36 ± 0.10	0.44 ± 0.11	0.48 ± 0.12	0.44 ± 0.10
B_{max}/K_d*				
FP	NA	3.19 ± 0.26†	3.69 ± 0.30	3.05 ± 0.24†
FN	NA	2.89 ± 0.39	3.53 ± 0.45	2.75 ± 0.41

Abbreviations: FN, family negative; FP, family positive; K_1, transport constant of radiotracer from plasma to tissue; NA, not applicable.
*See the "Methods" section for explanation.
†Comparison between FP and FN, $P<.05$.

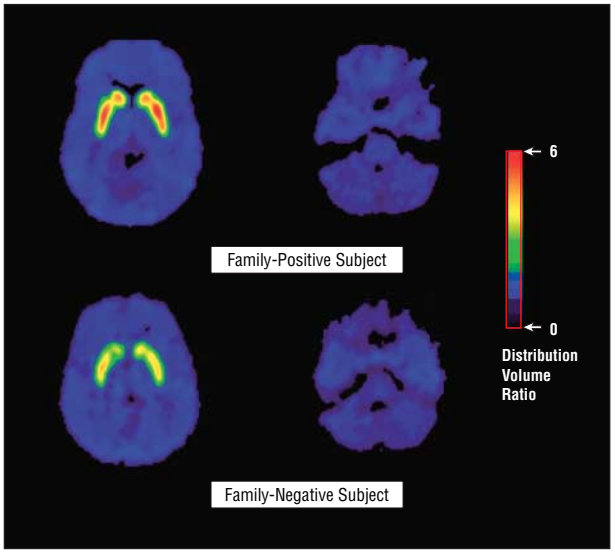

Figure 1. Images for the distribution volume ratios of carbon 11 (^{11}C)–labeled raclopride showing higher dopamine D_2 receptor availability in a family-positive than in a family-negative subject. Images shown correspond to levels where the striatum and cerebellum are visualized.

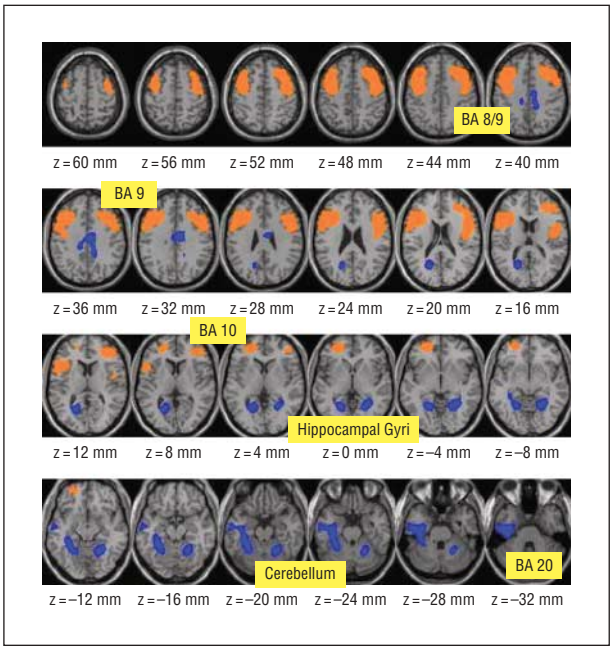

Figure 2. Statistical parametric mapping images showing regions where metabolism was higher in family-positive than in family-negative subjects (orange) and where metabolism was lower in family-positive than in family-negative subjects (blue) ($P<.05$, corrected, cluster size >100 voxels). BA indicates Brodmann area.

D_2 RECEPTOR AVAILABILITY IN FP AND FN SUBJECTS

Analysis of the [^{11}C]raclopride images showed no group differences in K_1 measures (transport constant of radiotracer from plasma to brain) in striatum or in cerebellum (**Table 2**). In contrast, the measures of D_2 receptor availability differed significantly between groups (**Figure 1**). The FP subjects had significantly higher measures of D_2 receptor availability in caudate ($P=.02$) and in ventral striatum ($P=.02$) than the FN subjects (Table 2).

To assess whether nicotine affected D_2 receptor availability, we also looked for differences between smokers and nonsmokers and found no differences for any of the striatal regions (data not shown).

REGIONAL BRAIN METABOLISM IN FP AND FN SUBJECTS

Comparison by SPM at $P<.05$ ("a priori hypothesis") showed that FP subjects had lower metabolism in hippocampal gyrus and cerebellum than FN subjects (**Figure 2**). It also showed lower metabolism in temporal pole (Brodmann area [BA] 20) and higher metabolism in prefrontal cortex (BA 8, 9, 10) in FP than FN subjects. However, these differences were not significant for the SPM comparison at $P<.005$ ("exploratory analysis").

CORRELATIONS BETWEEN D_2 RECEPTOR AVAILABILITY AND REGIONAL BRAIN METABOLISM

The pattern of correlations obtained between regional brain metabolism and striatal D_2 receptor with SPM (voxel level) was similar for the striatal regions (caudate, putamen, and ventral striatum). Thus, we averaged the D_2 receptor measures in the striatal regions to show the results for the correlations. The SPM performed at a significance level of $P<.05$ to test the a priori hypothesis

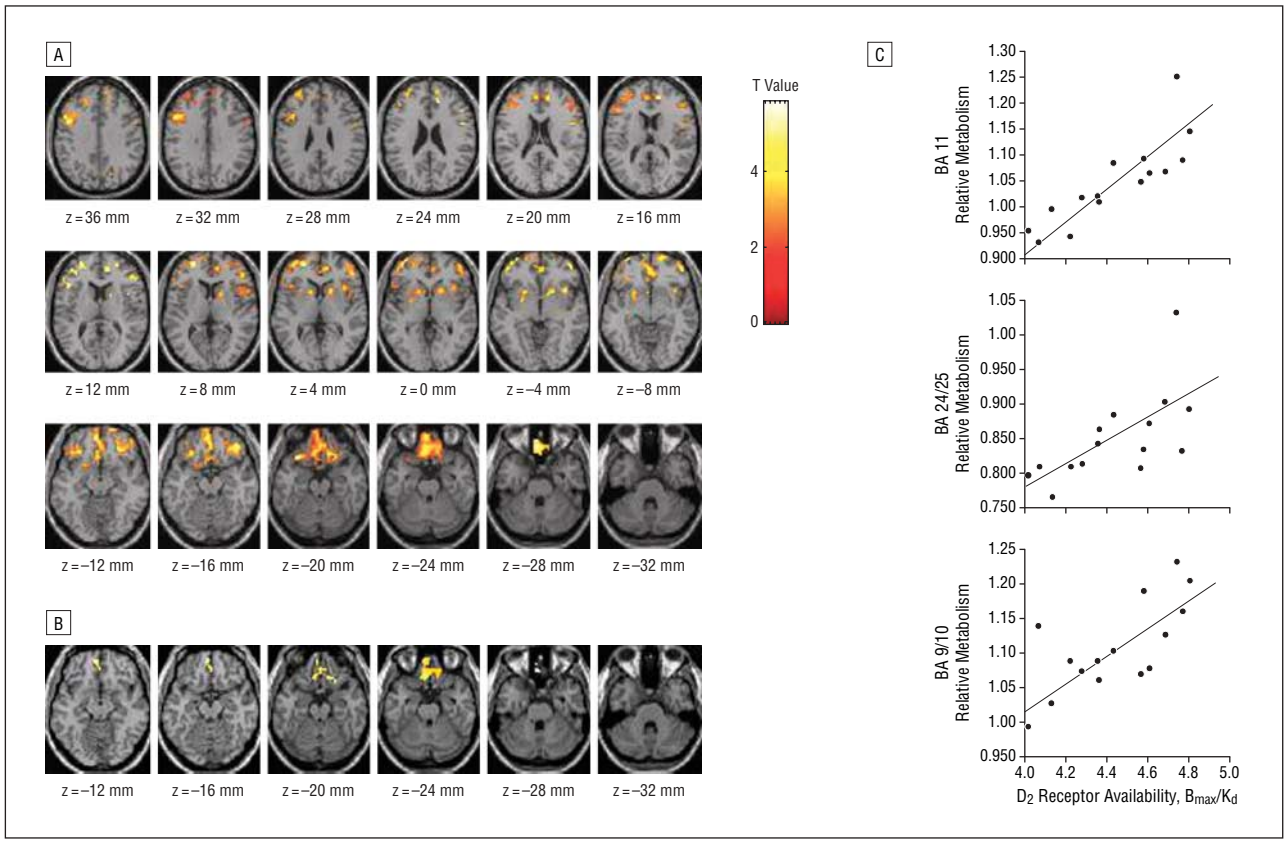

Figure 3. Correlations between dopamine D_2 receptor availability and regional brain metabolism. A, Statistical parametric mapping images for the family-positive subjects showing areas where metabolism was significantly correlated with D_2 receptor availability (B_{max}/K_d; see the "Methods" section for an explanation) in striatum ($P<.05$, corrected; cluster size, >100 voxels). B, Statistical parametric mapping results for the "exploratory analysis" showing only planes where differences were significant at $P<.005$ (corrected; cluster size, >100 voxels). C, Regression plots for the correlations between D_2 receptor availability in striatum and metabolic activity in orbitofrontal cortex (Brodmann area [BA] 11) ($r=0.85$; $P<.001$), ventral cingulate gyrus (BA 24/25) ($r=0.66$; $P<.008$), and prefrontal cortex (BA 9/10) ($r=0.72$; $P<.003$). The correlations in the family-negative subjects were not significant.

showed significant positive associations for the FP subjects between metabolism and striatal D_2 receptor in frontal cortical regions (including prefrontal cortex, anterior CG, and OFC) (**Figure 3**A). The SPM performed at a significance level of $P<.005$ for the exploratory analysis showed that the only significant correlation was with medial BA 11 (Figure 3B). These correlations were corroborated with ROI, which showed a positive correlation between striatal D_2 receptor and metabolism in OFC (BA 11) ($r=0.85$; $P<.001$), ventral CG (BA 24/25) ($r=0.66$; $P<.008$), and prefrontal cortex (BA 9/10) ($r=0.72$; $P<.003$) (Figure 3C, **Table 3**). For the FN group the correlations with D_2 receptor were not significant (Table 3).

CORRELATIONS BETWEEN D_2 RECEPTOR AVAILABILITY AND PERSONALITY MEASURES

The correlations between D_2 receptor and positive emotionality were significant for both FP subjects ($r=0.53$; $P=.05$) and FN subjects ($r=0.71$; $P=.02$). For the exploratory analysis, the correlations showed a trend with the constraint factor for the harm avoidance scale in FP subjects ($r=0.53$; $P=.05$) but not FN subjects ($r=0.17$; $P=.64$) and in the control scale in FP subjects ($r=0.51$; $P=.06$) but not FN subjects ($r=0.26$; $P=.47$).

CORRELATIONS BETWEEN REGIONAL BRAIN METABOLISM AND PERSONALITY MEASURES

The SPM performed at a significance level of $P<.005$ for the exploratory analysis showed that the correlations were significant for FP but not FN subjects. In FP subjects, scores on positive emotionality were significantly correlated with metabolism in left OFC (BA 11) (**Figure 4**A). These correlations were corroborated with ROI in left BA 11 ($r_{12}=0.71$; $P=.007$) (Figure 4B). The correlations with the negative emotionality and constraint factors were not significant.

COMMENT

D_2 RECEPTOR DIFFERENCES BETWEEN GROUPS

The significantly higher D_2 receptor availability in caudate and in ventral striatum in the FP group compared with the FN group corroborates our working hypothesis that a high D_2 receptor level in striatum is a protective factor against alcohol abuse. This assumes that, despite a family history of alcoholism, nonalcoholic members of alcoholic families may be enriched with protective factors, including high D_2 receptor availability, that com-

Table 3. Significant Correlations Between D_2 Receptors and Relative Regional Metabolism in FP and FN Subjects

	D_2 Receptors					
	Caudate		Putamen		Ventral Striatum	
Region	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value
FP Subjects						
OFC						
BA 11	0.69	.005	0.86	<.001	0.54	.04
CG						
BA 24/25	0.57	.03	0.63	.01	0.35	.21
Prefrontal						
BA 9	0.71	.003	0.62	.01	0.68	.005
BA 10	0.51	.06	0.51	.06	0.51	.06
FN Subjects						
OFC						
BA 11	0.30	.27	0.29	.27	0.18	.49
CG						
BA 24/25	0.17	.54	0.27	.31	0.20	.45
Prefrontal						
BA 9	0.05	.86	0.01	.99	0.12	.65
BA 10	0.11	.68	0.17	.52	0.31	.25

Abbreviations: BA, Brodmann area; CG, cingulate gyrus; FN, family negative; FP, family positive; OFC, orbitofrontal cortex.

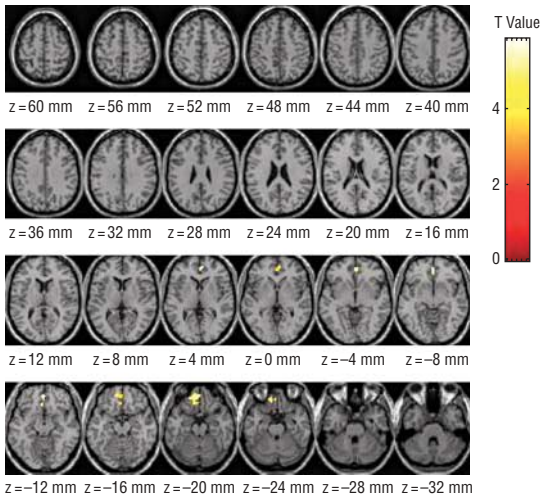

Figure 4. Correlations between regional brain metabolism and positive emotionality. Statistical parametric mapping images for the family-positive subjects showing areas where metabolism was significantly correlated with scores on positive emotionality ($P<.005$, corrected; cluster size, >100 voxels).

pensate for the higher inherited vulnerability. These results are in agreement with those reported by a PET study of siblings discordant for cocaine abuse[47] that showed not only that the cocaine-abusing sibling had a lower D_2 receptor level than a control group but also that the nonabusing sibling had a higher D_2 receptor level than the control group.

In the present study, it was not possible to determine whether high D_2 receptor availability in FP nonalcoholic subjects reflects underlying genetic or environmental factors or their interactions. There is evidence that genetic[48] as well as environmental[49] factors are involved in D_2 receptor expression. Moreover, in nonhuman primates, it has been shown that when social environmental factors result in high D_2 receptor levels, this is associated with protection, and when they result in low D_2 receptor levels, this is associated with a propensity to self-administer cocaine.[49] However, high D_2 receptor availability could also reflect a genetic modulation toward favorable responses to social stressors (ie, growing up in a household with an alcoholic parent).

In previous studies[22,23] we showed that in non–drug-abusing subjects D_2 receptor availability was associated with the reinforcing responses to the psychostimulant drug methylphenidate hydrochloride; subjects with low D_2 receptor availability tended to report an acute intravenous administration of methylphenidate as pleasant, whereas those with high D_2 receptor levels tended to report it as unpleasant. Also, a recent study documented that subjects with high D_2 receptor availability showed higher levels of intoxication after alcohol than subjects with low D_2 receptor levels, who showed blunted responses.[16] Inasmuch as subjects with blunted responses to alcohol have been shown to have a higher risk of alcoholism,[3] the latter study is also consistent with the hypothesis that high D_2 receptor availability may be protective. Moreover, preclinical studies have shown that in rodents trained to self-administer alcohol, D_2 receptor overexpression in nucleus accumbens markedly reduces alcohol intake both in rats that are genetically predisposed to self-administer alcohol (alcohol-preferring rats)[24] and in those that are not (Sprague-Dawley)[25]; this finding provides evidence that high D_2 receptor availability may interfere with alcohol intake, even in animals that are genetically prone to administering alcohol.

Further evidence of the involvement of D_2 receptor in alcohol preferences is given by findings of lower D_2 receptor levels in alcohol-preferring rats than in alcohol-nonpreferring rats,[10,14] and of increases in alcohol intake after microinjection of a D_2 receptor antagonist into the nucleus accumbens in alcohol-preferring rats.[50] Also,

D_2 receptor antagonists increase alcohol relapse rates in alcoholic subjects.[51] Thus, the current findings and those from the preclinical literature are compatible with the notion that D_2 receptor modulates the motivation to self-administer alcohol.

The D_2 receptor gene (in particular, the Taq 1 A1 polymorphism) has been one of the one most widely investigated and one of the most controversial in alcoholism.[52] Also controversial is the extent to which the Taq 1 A1 polymorphism affects the expression of D_2 receptor in the brain.[53] In the present study, we document an increase in D_2 receptor availability in unaffected FP individuals rather than a decrease, which is what is reported for alcoholics. This suggests that it is unlikely that genetically determined low expression of D_2 receptor underlies the inherited vulnerability to alcoholism but rather that low D_2 receptor levels in alcoholic subjects reflect a gene-environment interaction (including long-term alcohol abuse), while the increased D_2 receptor availability in nonalcoholic subjects provides a protective factor as they go through the age of risk.

REGIONAL BRAIN METABOLIC MEASURES

The SPM replicated our previous findings of reduced baseline cerebellar metabolism in FP subjects.[38] In that study we also reported that a group of FP subjects showed a blunted cerebellar response to the benzodiazepine drug lorazepam, which led us to postulate that the cerebellar findings in this group could reflect differences in $GABA_A$-benzodiazepine receptors. The hippocampal gyrus, which in the present study was also found to have reduced metabolism in the FP subjects, is a brain region that similarly contains a high density of $GABA_A$ receptors.[54] Thus, these findings are compatible with recent genetic studies reporting an association between alcoholism and the $GABA_A$ receptor gene.[55]

RELATIONSHIP BETWEEN D_2 RECEPTOR AND METABOLISM IN OFC, CG, AND PREFRONTAL CORTEX

The significant association between D_2 receptor levels and metabolic measures in OFC and CG in FP subjects is similar to what we had previously reported in cocaine- and methamphetamine-addicted subjects in whom higher levels of D_2 receptor were associated with higher metabolic activity in OFC and anterior CG.[30] Because the OFC and CG are involved with inhibitory control,[29] we had postulated that the improper regulation by DA of these regions in addicted subjects could underlie their loss of control and compulsive drug intake.[56] Indeed, in alcoholic subjects reductions in D_2 receptor availability in ventral striatum have been shown to be associated with alcohol craving severity and with greater cue-induced activation of the medial prefrontal cortex and anterior CG as assessed with functional magnetic resonance imaging.[20] The observed association between D_2 receptor and OFC and anterior CG confirmed our hypothesis that the effects of D_2 receptor on vulnerability to addiction may be mediated by activity in brain regions that control inhibitory and emotional responses.

In addition, we showed in FP subjects an association between D_2 receptor and activity in prefrontal cortex (BA 9/10). Imaging studies have consistently shown an involvement of the prefrontal cortex in emotional processing.[57] It is postulated that emotional information from limbic regions is conveyed to the prefrontal cortex, where conscious and voluntary emotional self-regulation occurs.[58] Indeed, activation of the prefrontal cortex and of ventral CG (BA 24/25) has been documented with conscious suppression of sexual arousal[59] and of sadness.[58] Thus, enhanced dopaminergic signaling through D_2 receptor could protect against alcoholism by favoring control over emotional reactions.

The association between striatal D_2 receptors and metabolism in OFC, CG, and prefrontal cortex could reflect either striatal modulation of frontal regions via striatothalamocortical projections[60] or frontal modulation of striatal regions by glutamatergic frontomesencephalic and frontostriatal projections.[61] Most of the D_2 receptor–containing neurons in striatum are GABAergic, and DA signals in striatum are transferred to cortical regions via GABAergic pathways, which are inhibitory.[62] Because a factor that has been associated with inherited vulnerability to alcoholism is impairment in inhibitory neurotransmission,[63] high D_2 receptor levels could exert a protective effect by increasing modulation of GABA cells and thus compensating for this deficit.

RELATIONSHIP BETWEEN D_2 RECEPTOR, REGIONAL BRAIN METABOLISM, AND PERSONALITY MEASURES

It is likely that the inherited vulnerability to alcoholism is not specific to this drug. Instead, it has been postulated that what is inherited are personality characteristics (eg, novelty seeking, disinhibition) that are associated with alcohol abuse.[64] In this study, the FP group had lower scores than the FN group in measures of positive emotionality[65] and showed a trend toward a decrease in the scores of self-control. Because individuals scoring low on positive emotionality have higher thresholds for the experience of positive emotions and for positive engagement with their social environment, one could postulate that this could put them at risk for alcohol abuse as a means to compensate for this deficit. Indeed, a common expectation for alcohol's effects is facilitating interpersonal closeness and the pleasure from social interactions.[66]

The positive emotionality measures were also correlated with activity in left BA 11. Because D_2 receptor availability in striatum was also associated with metabolism in BA 11, this could be a neurobiological substrate through which DA via D_2 receptor could modulate positive emotional responses and protect against alcohol abuse. In addition, the association of D_2 receptor with dorsolateral frontal cortex could also protect by favoring cognitive control over emotional responses.

LIMITATIONS

In this study we show that unaffected members of families with a history of alcoholism may have a protective factor, namely, high D_2 receptor availability. However,

we cannot rule out the possibility that the FP subjects were not alcoholics because they did not inherit the vulnerability genes.

This study reports a 10% difference in the availability of D_2 receptor between FP and FN subjects. Even though this may seem like a modest difference, it is equivalent to what we have reported between subjects who show pleasant vs aversive responses to the stimulant drug methylphenidate.[22] Also, in studies of normal aging, we have shown that a 10% difference in D_2 receptor is associated with 12% difference in locomotor speed,[67] suggesting that a 10% D_2 receptor difference is functionally significant.

We interpret the increases in D_2 receptor availability as reflecting increases in the levels of receptors. However, because [^{11}C]raclopride is sensitive to competition with endogenous DA, we cannot rule out the possibility that FP subjects could have decreases in DA release that result in high D_2 receptor availability. This interpretation is less likely, since endogenous DA is estimated to occupy, under baseline conditions, 10% of D_2 receptors,[68] which is equivalent in magnitude to the difference observed between the FP and the FN groups. This would mean that FN subjects would have to have double the baseline levels of endogenous DA of FP subjects, ie, levels equivalent to those reported in schizophrenic subjects in whom these high DA levels are associated with psychoses.[68] However, we cannot rule out the possibility that the inherited vulnerability is a decrease in baseline DA for which FP subjects compensate by up-regulating D_2 receptor.

The correlation between D_2 receptor and OFC and CG metabolism was observed in FP but not FN subjects, and whereas D_2 receptor levels are higher in FP than FN subjects, metabolism in OFC and CG is not. It would therefore appear that, in FP subjects, high D_2 receptor availability is required to maintain metabolic levels in OFC and CG comparable to those in FN subjects. Thus, we cannot rule out the possibility that the high D_2 receptor availability in FP subjects may reflect a compensation for a primary deficit in OFC and CG.

The mean age of the FP group was 24 years. An examination of the data from the Collaborative Study on the Genetics of Alcoholism, which consists of a large sample of densely affected alcohol-dependent families, showed that when offspring of probands who meet *DSM-IV* criteria for alcohol reach 24 years of age, 83.5% of those who will develop alcohol dependence have already done so (Bernice Porjesz, PhD, Henri Begleiter, MD, Laura Bierut, MD, unpublished data, 2006). Thus, it is plausible that 15% to 20% of the FP subjects could still become alcoholics. Also, these results do not imply that high D_2 receptor levels in these subjects will protect them for the rest of their lives; D_2 receptor levels in brain are sensitive to social stressors and drug exposure (reviewed by Nader and Czoty[69]) and thus are likely to change differently throughout the life span of individuals. Prospective studies will enable us to determine whether nonalcoholic FP subjects will become alcoholics later in life and to evaluate whether this is associated with a reduction in D_2 receptor levels.

Finally, in this study we did not exclude smokers. However, the facts that the 2 groups did not differ in the percentage of smokers and there were no differences in D_2 receptor levels between smokers and nonsmokers suggest that nicotine does not drive the findings.

CONCLUSIONS

The finding of high D_2 receptor availability in subjects who are not alcoholic, despite risk of alcoholism due to family history, supports the hypothesis that high D_2 receptor levels exert a protective effect against alcoholism. The positive association between D_2 receptor availability and metabolism in OFC, CG, and prefrontal cortex, which are regions involved with inhibitory control, emotional reactivity, and executive function, as well as with personality measures of positive emotionality, suggests that cognitive and emotional processes may be mechanisms underlying the protective effects of high D_2 receptor levels.

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Correction

Errors in Table and Figure. In the Original Article by Giesen-Bloo et al titled "Outpatient Psychotherapy for Borderline Personality Disorder: Randomized Trial of Schema-Focused Therapy vs Transference-Focused Psychotherapy," published in the June issue of the ARCHIVES (2006;63:649-658), there were several errors in **Table 1**. The table is reprinted correctly as follows. Furthermore, neither recent suicide planning, steps, or attempts nor recent nonsuicidal self-injury were significantly related to recovery from borderline personality disorder or changed the difference between schema-focused therapy and transference-focused psychotherapy when these variables were entered alone or in combination in the survival analyses. In all analyses, schema-focused therapy remained superior to transference-focused psychotherapy. Treatment group by suicidal or self-injury manifestation interaction was not significant. In addition, the x-axis label in Figure 3A, B, and C should have been "Assessment" rather than "Month." The ARCHIVES regrets these errors.

Table 1. Sociodemographic and Clinical Characteristics of 86 Study Participants[a]

	Schema-Focused Therapy Group (n = 44)	Transference-Focused Psychotherapy Group (n = 42)	*P* Value
Age, mean (SD), y	31.70 (8.89)	29.45 (6.47)	.15[b]
Women	40 (90.9)	40 (95.2)	.43[b]
Education			
Graduate/professional	6 (13.6)	4 (9.5)	
College graduate	3 (6.8)	7 (16.7)	
Some college	17 (38.6)	14 (33.3)	.22[b]
High school graduate	5 (11.4)	10 (23.8)	
Grades 7-11	13 (29.6)	7 (16.7)	
Employment status			
Housewife	8 (18.2)	5 (11.9)	
Student	3 (6.8)	6 (14.3)	
Employed	9 (20.5)	8 (19.0)	.89[b]
Disability	17 (38.6)	17 (40.5)	
Welfare	7 (15.9)	6 (14.3)	
Psychotropic medication use at baseline	34 (77.3)	30 (71.4)	.87[b]
Recent suicide planning, steps, or attempts[c]	17 (38.6)	24 (57.1)	.09[b]
Recent nonsuicidal self-injury[d]	21 (47.7)	32 (76.2)	.007[b]
Meeting *DSM-IV* BPD criterion 5	31 (70.5)	33 (78.6)	.39[b]
Childhood sexual abuse[e]	31 (70.5)	26 (61.9)	.40[b]
Childhood physical abuse[e]	40 (90.9)	37 (88.1)	.67[b]
Childhood emotional abuse or neglect[e]	42 (95.5)	37 (88.1)	.21[b]
No. of Axis I diagnoses, mean (SE) [95% CI]	2.95 (0.23) [2.49-3.42]	2.40 (0.25) [1.89-2.92]	.11[f]
No. of Axis II diagnoses (BPD included), mean (SE) [95% CI]	2.14 (0.18) [1.78-2.49]	2.05 (0.18) [1.68-2.42]	.73[f]
No. of SCID II BPD criteria, mean (SE) [95% CI]	6.70 (0.16) [6.38-7.03]	7.12 (0.19) [6.72-7.52]	.23[f]
No. of treatment modalities before baseline, mean (SE) [95% CI][g]	3.00 (0.19) [2.61-3.39]	2.79 (0.20) [2.38-3.20]	.45[f]

Abbreviations: BPD, borderline personality disorder; BPDSI-IV, Borderline Personality Disorder Severity Index, fourth version; CI, confidence interval; SCID II PD, Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders.
[a]Data are given as number (percentage) except where otherwise indicated.
[b]Based on the Pearson χ^2 test.
[c]According to BPDSI-IV items 5.11 to 5.13 in the previous 3 mo.
[d]According to BPDSI-IV items 5.1 to 5.8 in the previous 3 mo.
[e]Assessed using the structured childhood trauma interview.
[f]Based on analysis of variance.
[g]Range, 0 to 6; individual treatment, group treatment, family/couples therapy, daily medication, clinical treatment, and otherwise.